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The Role of Cyclosporine A in the Treatment of Prosthetic Vascular Graft Infections with the Use of Arterial Homografts

Artur Pupka and Tomasz Płonek
Wroclaw Medical University
Poland

1. Introduction

Infections of prosthetic grafts in vascular surgery are the cause of many serious postoperative complications including death (Bahnini et al.,1991; Callow,1996; Wilson,2001; Yeager&Porter,1992). Encouraging results were obtained when cold-preserved fresh arterial homografts and other biologic grafts were used to replace infected prosthetic grafts (Chiesa et al.,1998, 2002). Cooling down the grafts only to 4^{O}C allows preservation of the arterial endothelium. However, the endothelium is immunogenic, and thus immunosuppression is needed (Cerilli et al.,1985; Methe et al.,2007; Paul et al.,1985; Pober et al.,1984). Moreover, organ donors should be selected with respect to histocompatibility and blood group types (Gabriel et al.,2002; Mirelli et al.,1998, 1999; Scolari et al.,1998). Experimental studies show that immunosuppressive treatment is helpful after the implantation of cold-preserved fresh arterial homografts (Azuma et al.,1999; Gabriel&Fandrich,2002). On the other hand, there is a concern that immunosuppressive drugs can exacerbate the infection. There are no clinical studies examining the need to use immunosuppression after the transplantation of fresh arterial homografts in prosthetic graft infections (Mirelli et al.,1999). We assumed that administration of Cyclosporine A with a concomitant antibiotic therapy may improve the viability of the fresh arterial homografts and improve the patients' condition.
One of the diagnostic methods used to detect infections in vascular surgery is scintigraphy with the use of Technetium-99m labeled leucocytes. Leucocytes migrate and accumulate in the infected area allowing for the area of accumulation to be estimated (Plissonnier et al.,1995). Objective monitoring of the infection after an arterial graft implantation facilitates the decision of choosing the right treatment, especially for patients treated with immunosuppressive drugs.
The aim of our study was to assess the influence of Cyclosporine A administration on the outcome of patients who underwent fresh arterial homograft transplantation in the treatment of prosthetic graft infections.

2. Materials and methods

2.1 Study design

We carried out a prospective, non-randomized observational study. 79 patients were admitted to our clinic between March 2001 and January 2009 due to a prosthetic graft

infection. In all cases we observed infection of the prosthetic graft with purulent fistulas, fluid spaces around the prostheses and bleeding from the vascular anastomoses. All patients that could not wait for the fresh arterial homograft had the prosthesis replaced with a silver coated prosthesis (27 patients). 52 patients who could wait for the arterial homograft were put on a waiting list and were treated with antibiotics and local disinfectants until they had the infected prosthesis replaced with an arterial homograft. According to the protocol approved by the Ethics Committee of the University of Medicine of Wroclaw, patients decided whether they wanted to take Cyclosporine A after obtaining detailed information about the possible benefits and risks of taking this medication. We defined early and late postoperative periods as ≤30 days and >30days respectively. The patients were divided into 2 groups: Group 1 – consisting of 26 patients who received 1-3 mg/kg of Cyclosporine A per day with dose adjustments to maintain a serum concentration of 120-140 mg/ml and group 2 - consisting of 26 patients who were treated without immunosuppressive drugs (Table 1). All patients with positive cross-match were assigned to group 1 (3 patients).

Characteristics of homograft recipients	Group 1 (N=26)	Group 2 (N=26)
Age (years, mean+-SD)	42-68 (57±1)	50-71 (59±5)
Male	25	24
Female	1	2
Additional illnesses		
Diabetes	8 (30%)	8 (31%)
Ischemic heart disease	15 (58%)	14 (54%)
Renal failure	4 (15%)	4 (15%)
Leg necrosis	7 (27%)	6 (23%)
Graft-duodenal fistula	6 (23%)	5 (19%)

Table 1. Characteristics of homografts recipients

In each case, the infection was confirmed with Duplex- Doppler Ultrasound, CT and scintigpraphy using Technetium-99m labeled leucocytes. The patients received antibiotics (vancomycin, ciprofloxacin, imipenem) according to the antibiogram, usually for a period of up to 30 days after the operation.

All of the homografts were evaluated before the implantation using scanning electron microscopy. In each case, the examination revealed a non-damaged arterial wall and the presence of the endothelium.

Immunological characteristics of patients qualified for an arterial transplantation		
Homograft	Group 1 (N=26)	Group 2 (N=26)
ABO compatibility	26 (100%)	26 (100%)
Negative cross-match	23 (88%)	26 (100%)
Number of incompatibilities in HLA (average+-SD)	3.7±1.8	3.7±1.5
Negative virological examination in donor	26 (100%)	26 (100%)
Time of graft's preservation (hrs, average+-SD)	6-24 (15.2±4.8)	8-22 (14.4±4.9)

Table 2. Immunological characteristics of patients qualified for an arterial transplantation

2.2 Patients

2.2.1 Group 1

The administration of Cyclosporine A (Sandimmun®; Novartis Pharma GmbH) began intraoperatively after revascularization. In this group, 21 Y-shaped, 4 ilio-femoral and 1 aorto-femoral cold-preserved fresh arterial grafts were implanted. The time of simple hypothermia preservation of aortic allografts did not exceed 24 hours. 3 patients from this group had slightly positive cross-match results with the donors' lymphocytes. Microbiological cultures from the specimens from the groin, retroperitoneal space and the infected prosthesis revealed MRSA (24 patients; 92 %), *Staphylococcus epidermidis* (10; 38%) and *Pseudomonas aeruginosa* (7; 27%) infections.

2.2.2 Group 2

In group 2, 22 bifurcated and 4 ilio-femoral arterial allografts were implanted. The time of homograft preservation did not exceed 22 hours. Bacteriological cultures confirmed the infection with MRSA (21 patients; 81%), *S.epidermidis* (9; 35%) and *P.aeruginosa* (5; 19%).

2.3 Homografts

There was no statistical difference in tissue histocompatibility between both groups (Table 2). Arterial homografts were collected from dead donors with a confirmed brain death. During this procedure, a fragment of an artery was taken for a microbiological and microscopic evaluation. Homografts were preserved in the UW (University of Wisconsin) fluid. Just before the operation, the tissues surrounding the allograft were removed and smaller arterial branches were tied up using monofilament sutures.

2.4 Methods

The postoperative treatment (the course of infection and the effects of the therapy), was monitored using scintigraphy. Before and after the operation, computed tomography (CT), duplex-doppler ultrasound, and in some cases, angiography were performed. Microbiological examination, tissue histocompatibility (A and B locus from class I HLA and D locus from class II HLA), ABO compatibility and cross-matches were carried out in every patient. The activity of CD3+, CD4+ and CD8+ lymphocytes was measured before and after the vascular procedure on the 1st, 3rd, 7th day, and in the 1st, 3rd, 6th, 12th, 18th and 24th month after the operation. Virological and serological examinations were performed in each donor (anty-HIV, HBs-Ag, anty-HBc, anty-HCV, anty-EBV, Hbe-Ag, anty-CMV, VDRL test).

The primary endpoint was the recurrence of infection confirmed by clinical and laboratory examinations or by scintigraphy. Secondary endpoints were early and late postoperative mortality and morbidity, amputations, graft patency, rupture of the graft and presence of the graft aneurysm.

2.5 Statistical analysis

Statistical analysis was performed with the use of Statistica 9,0 software. The results were analyzed by parametrical and non-parametrical tests such as chi-square, chi-square analysis of variance (ANOVA) and the U test of Mann-Whitney. Statistical significance was assumed at $p<0.05$.

2.6 Ethical approval for research

The protocol of this study was approved by the Ethics Committee of the University of Medicine of Wroclaw.

3. Results

52 patients were enrolled into the study. The mean ± standard deviation (SD) follow-up was 23.3 ± 6.1 months in group 1 and 19.2 ± 10.7 months in group 2. A long-term follow up was completed for 15 patients from group 1 and 14 from group 2.

3.1 Postoperative morbidity and mortality

3.1.1 Postoperative mortality

In group 1, one (4%) patient with an aorto-duodenal fistula died 14 days after the operation due to septic shock and one (4%) died 11 months after the operation due to a cerebrovascular accident. In group 2, four (15%) patients died in the early postoperative period. Two patients (8%) died due to a graft-duodenal fistula on the 5th and 19th postoperative day, one (4%) in the course of septic shock (3rd day) and one (4%) due to myocardial infarction (7th day). Two (8%) patients died in the late postoperative period due to rupture of the allograft (4th and 5th postoperative month) (Table 3, Fig.1). The mortality was higher in group 2 (23%) than in group 1 (8%), but this difference failed to reach statistical significance ($p>0.05$).

Postoperative mortality	Group 1 (N=26)	Group 2 (N=26)
Early<30 days		
Septic shock	1 (4%)	1 (4%)
Graft-duodenal fistula	-	2 (8%)
Myocardial infarction	-	1 (4%)
	1 (4%)	**4 (15%)**
Late>30 days		
Rupture of graft	-	2 (8%)
Cerebrovascular accident	1 (4%)	-
	1 (4%)	**2 (8%)**

Table 3. Postoperative mortality

3.1.2 Postoperative morbidity

In the group treated with cyclosporine, three (12%) early complications (graft thrombosis, wound dehiscene with evisceration, a hematoma in the inquinal area) and three (12%) late complications (symptoms of bowel ischemia, lower extremity ischemia, tibial arteries occlusion) were observed. Graft aneurysms or late thrombosis of the transplanted artery were not detected in this group. In the group treated without immunosuppression, there were no early complications and 9 (35%) late complications (MRSA inferction of the homograft, 5 cases of homograft aneurysms of which 3 ruptured and 3 femoral amputations due to graft thrombosis) (Table 4). The incidence of late postoperative complications was statistically greater in group 2 than in group 1 ($p=0.030$). There was no statistically

significant difference between group 1 and 2 in the occurrence of early postoperative complications and in the number of both early and late complications.

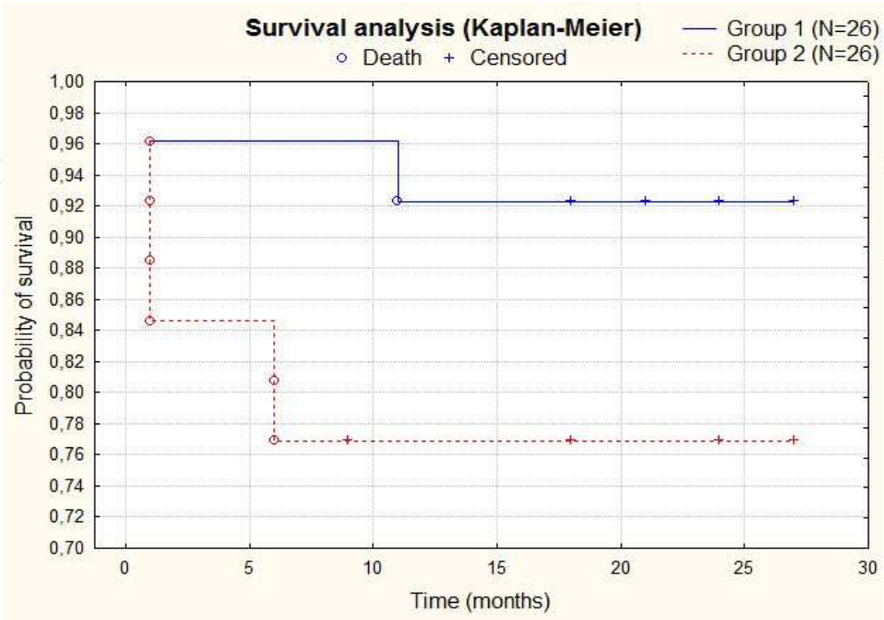

Fig. 1. Kapalan-Meier survival analysis of the patients

Postoperative morbidity	Group 1 (N=26)	Group 2 (N=26)
Early<30 days		
Infection of postoperative wound	1 (4%)	-
Graft thrombosis	1 (4%)	-
Hematoma	1 (4%)	-
	3 (12%)	**0 (0%)**
Late>30 days		
Graft infection	-	1 (4%)
Graft thrombosis - amputation	-	3 (12%)
Low extremity ischemia	2 (8%)	-
Graft aneurysm	-	2 (8%)
Symptoms of bowel ischemia	1 (4%)	-
Rupture of graft	-	3 (12%)
	3 (12%)	**9 (35%)**

Table 4. Postoperative morbidity

3.2 Laboratory and radiological examinations

In both groups, laboratory and radiological examinations confirmed the regression of the infection after the arterial graft implantation. Acute phase proteins were within normal range. The ultrasound examination showed no evidence of fluid spaces around the homografts. Scintigraphy revealed the statistically significant (p=0.011) decrease of

accumulation of the Tc-99m labeled leucocytes around the allograft in both groups during the whole observation period of 27 months. The biggest drop in the area of accumulated leucocytes was in the 6th postoperative month in both groups. The rate of the decrease was slightly greater in the group without immunosuppression, but this difference did not reach statistical significance.

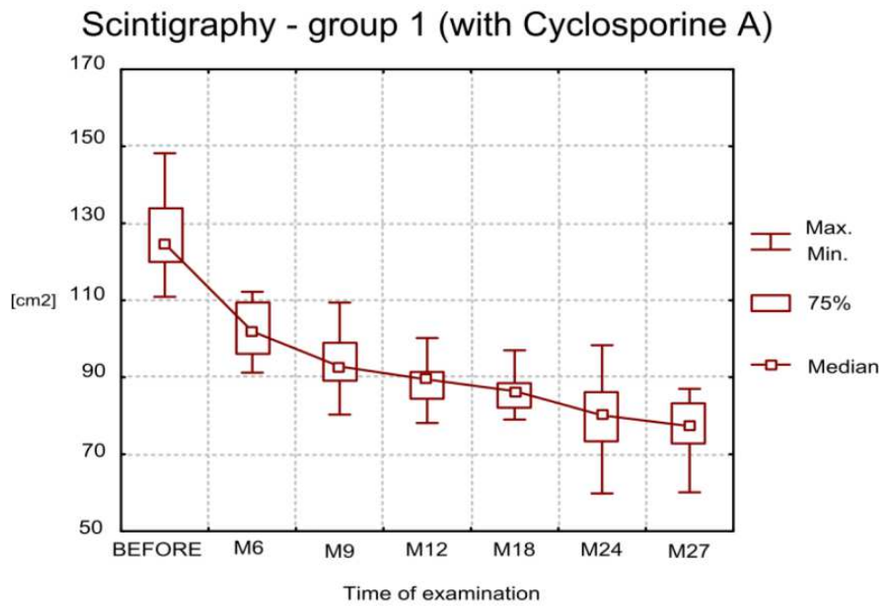

Fig. 2. The reduction of the area of accumulation of Tc99-labelled lymphocytes in patients from group 1 (with Cyclosporine A)

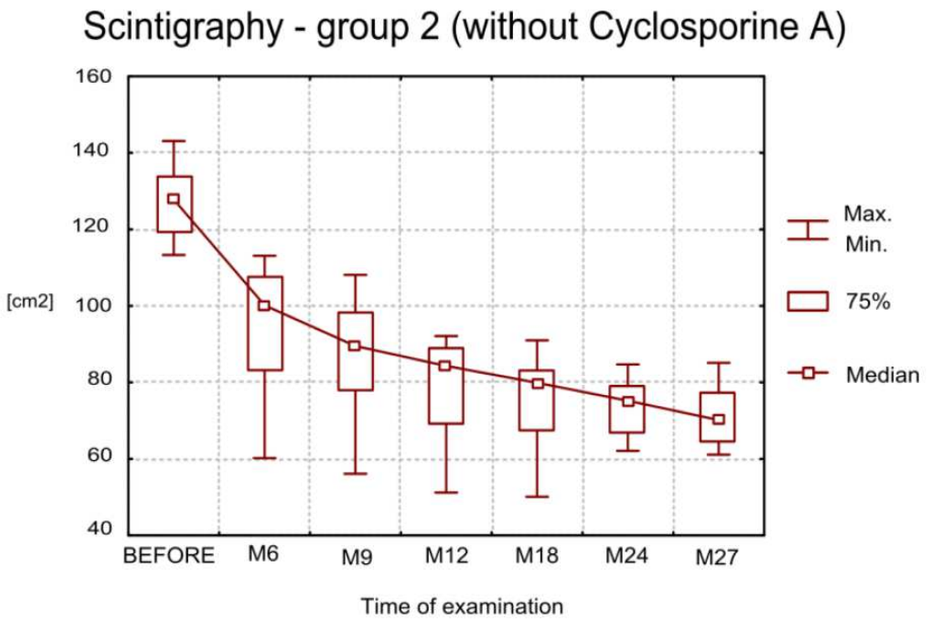

Fig. 3. The reduction of the area of accumulation of Tc99-labelled lymphocytes in patients from group 2 (without Cyclosporine A)

The total reduction of the area of accumulation of the Tc-99m labeled leucocytes during the postoperative period was 35% in group 1 and 44% in group 2 (Fig. 2,3). The statistically significant (p=0.016) difference between both groups in the area of accumulation was observed 18 months after the operation, and it was bigger in group 2.
When there was an increase or no decrease of the leucocytes accumulation, antibiotics were administered according to the antibiogram. This took place 4 times in group 1 (15%) and 3 times in group 2 (12%). The antibacterial treatment resulted in the reduction of the leucocytes accumulation and there were no further clinical signs of reinfection.

3.3 The activity of CD3+, CD4+ and CD8+ lymphocytes in blood

The analysis of the immunological response in both examined groups revealed an increase in the activity of CD3+ and CD4+ lymphocytes and a decrease in the activity of CD8+ lymphocytes. The increase in activity of CD3+ lymphocytes in group 1 was observed from the first postoperative day and it was statistically significant (p=0.04). The increase in activity of CD3+ lymphocytes was greater in group 2 than in group 1, and reached its maximal value on the 7th postoperative day (Fig.4,5). This difference in activity was also statistically significant (p=0.038). Statistical differences in CD3+ lymphocyte activity between both groups began in the sixth postoperative month and lasted until the 24th month (p=0.027).

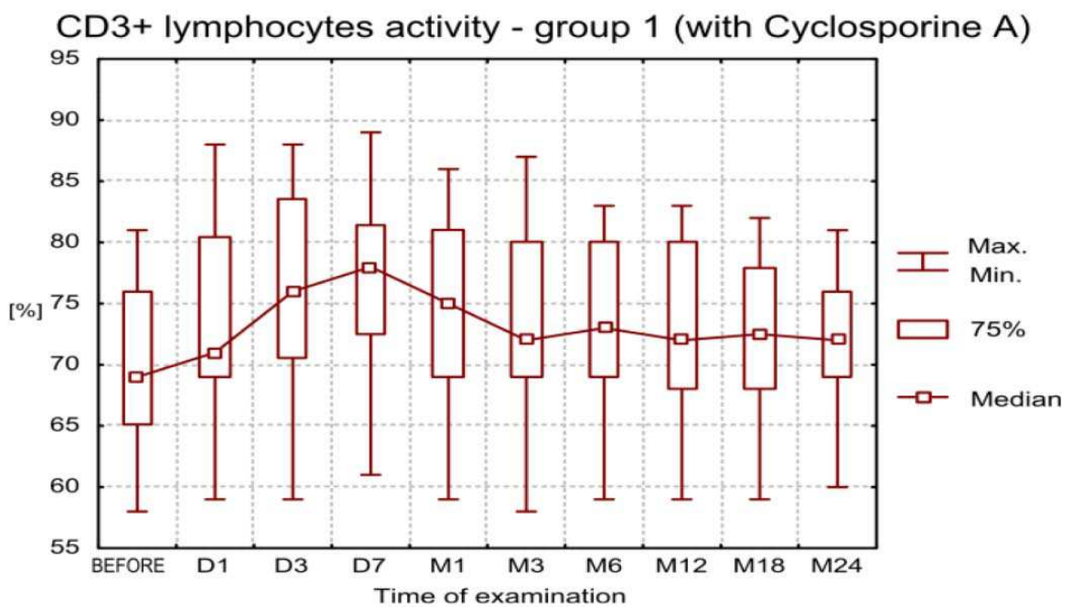

Fig. 4. The CD3+ lymphocytes' activity in patients from group 1 (with Cyclosporine)

The increase in activity of CD4+ lymphocytes was larger in group 2 than in group 1 (Fig. 6,7). The change in activity of CD4+ lymphocytes in both groups was statistically significant (p=0.035). The maximum activity was noted on the 7th postoperative day. A statistically significant difference in activity of CD4+ lymphocytes between both groups was seen on the first day (p=0.032) and in the third month after the arterial graft implantation (p=0.041).

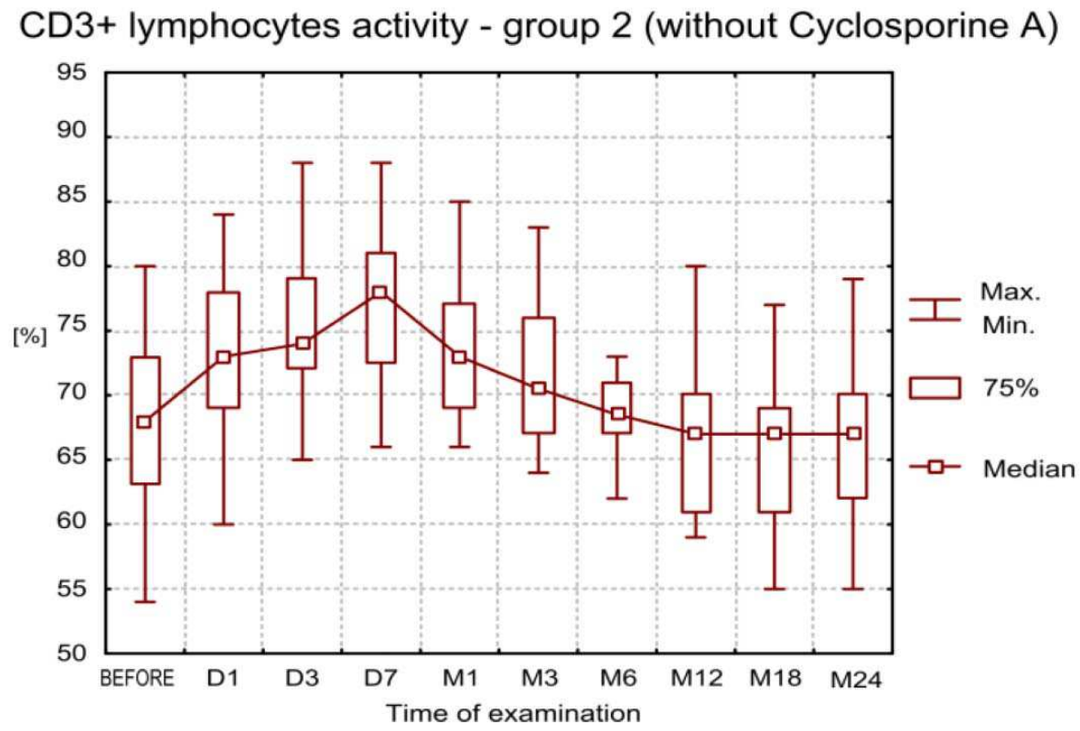

Fig. 5. The CD3+ lymphocytes' activity in patients from group 2 (without Cyclosporine)

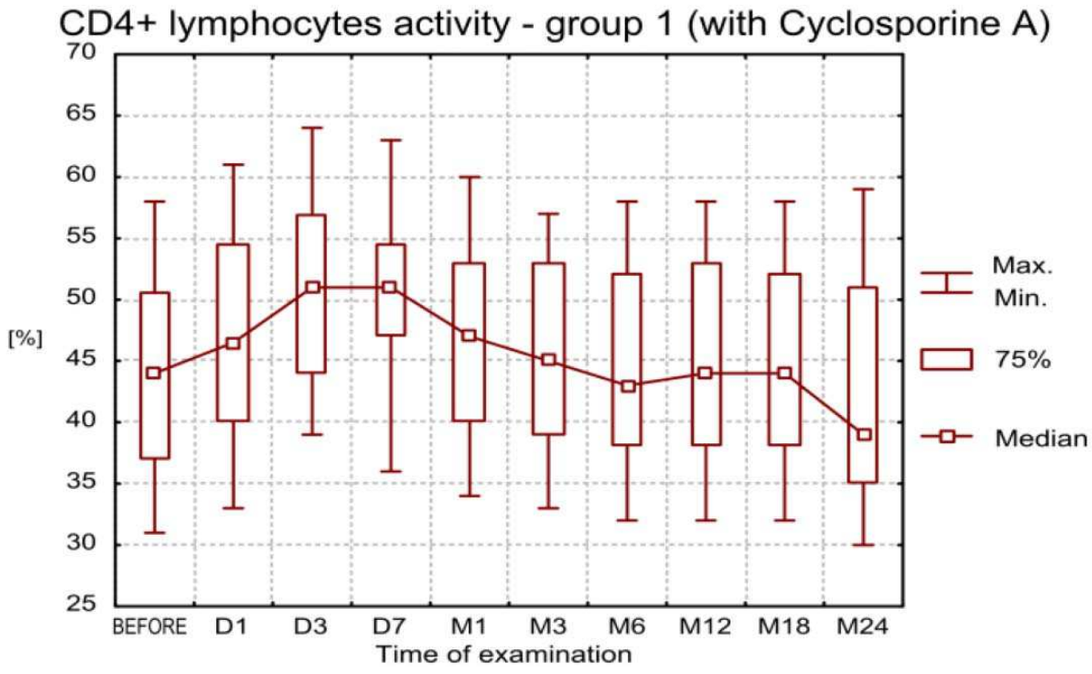

Fig. 6. The CD4+ lymphocytes' activity in patients from group 1 (with Cyclosporine)

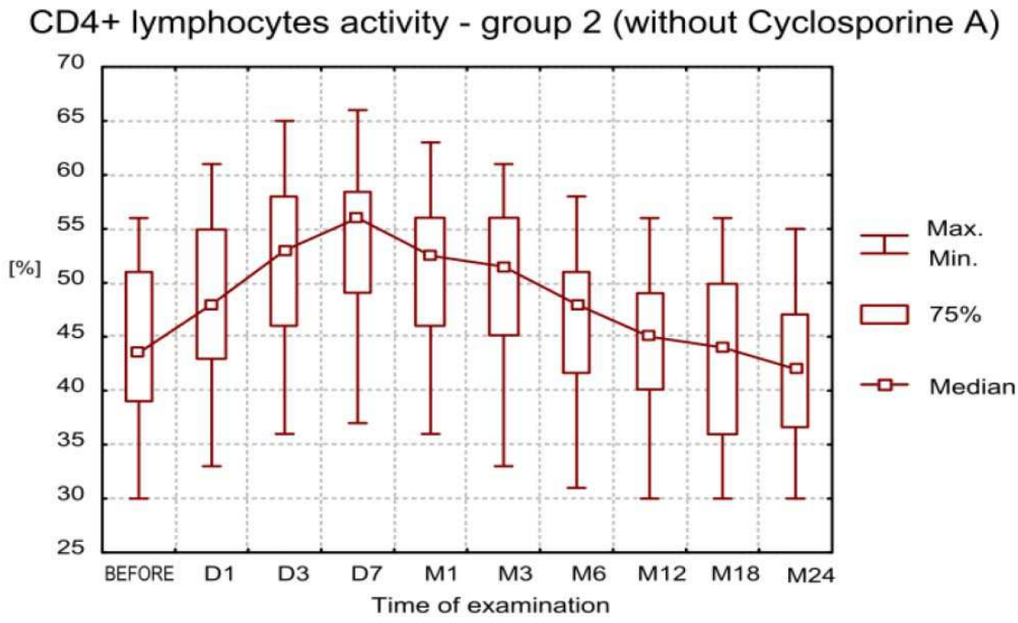

Fig. 7. The CD4+ lymphocytes' activity in patients from group 2 (without Cyclosporine)

The decrease in activity of CD8+ lymphocytes was at its maximum on the 7th day in group 1 and in the 1st month in group 2 after the operation (Fig. 8,9). This decrease was statistically significant (p=0.02) in both examined groups. The difference in activity of these leucocytes between group 1 and 2 was statistically significant (p=0.016) in the 18th month of the observation and was greater in group 2.

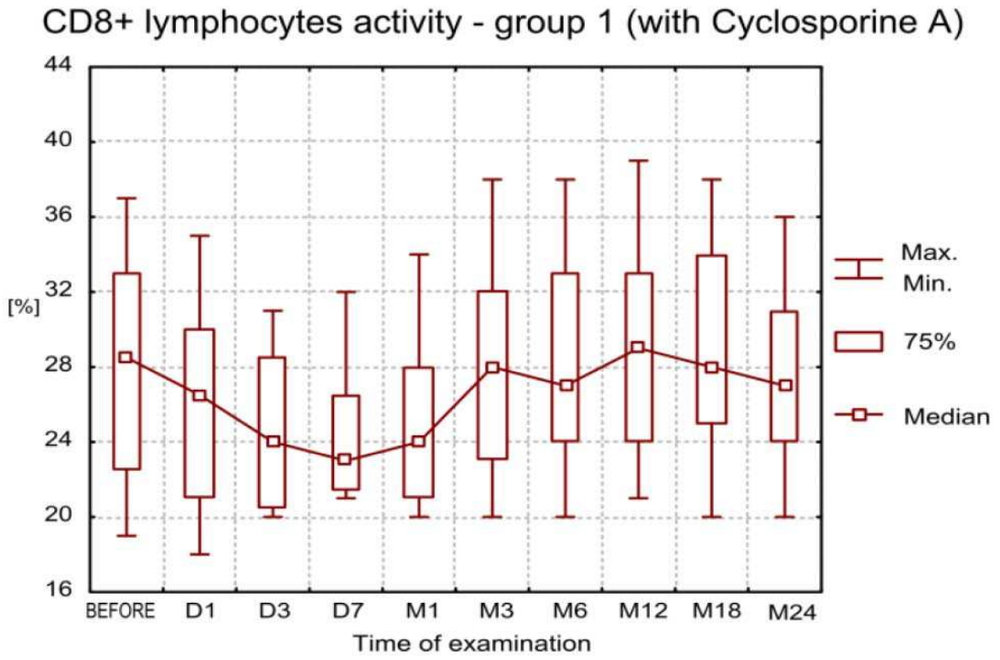

Fig. 8. The CD8+ lymphocytes' activity in patients from group 1 (with Cyclosporine)

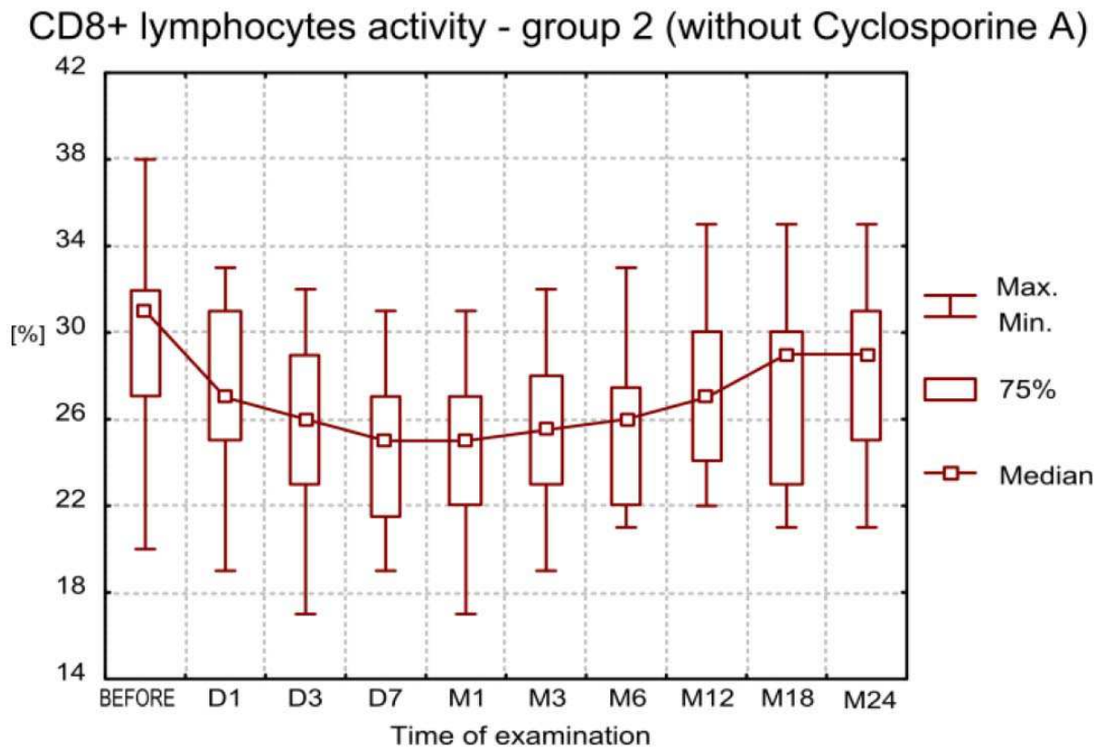

Fig. 9. The CD8+ lymphocytes' activity in patients from group 2 (without Cyclosporine)

3.4 Scanning electron microscopy

Scanning electron microscopy examinations were performed in two patients. One patient from group 1 and another one from group 2 had the arterial homografts removed due to late postoperative complications. The tissue specimens were prepared in the usual manner and assessed by an experienced histologist.

9 months after the transplantation, we collected a fragment of the ilio-femoral homograft from a patient from group 2, who had the transplanted artery removed due to an MRSA infection and rupture of the graft. Scanning electron microscopy (SEM) revealed a complete destruction of the homograft's wall - absence of the endothelium, single, damaged cells and cell fragments of the medial membrane (Fig.11).

We collected a fragment of the artery from a patient from group 1, who was operated on 13 months after the homograft implantation due to an arterial embolism. SEM showed the presence of the endothelial cells (which were mechanically detached), the intimal wall with thickened elastic lamina, a large amount of elastic and collagen fibres, fibrin inclusions, active myoblasts and myofibroblasts (Fig.10). The above mentioned patient stopped taking prescribed immunosuppressive drugs and was admitted to the hospital 12 months after the previous embolectomy. He suffered from lower extremity ischemia in the course of an arterial homograft embolism. Thrombectomy was carried out but this procedure did not improve the blood supply to the leg. Consequently, an amputation was performed. During this operation, a fragment of the arterial homograft's wall was collected. SEM revealed the absence of endothelial cells and the presence of cell apoptosis.

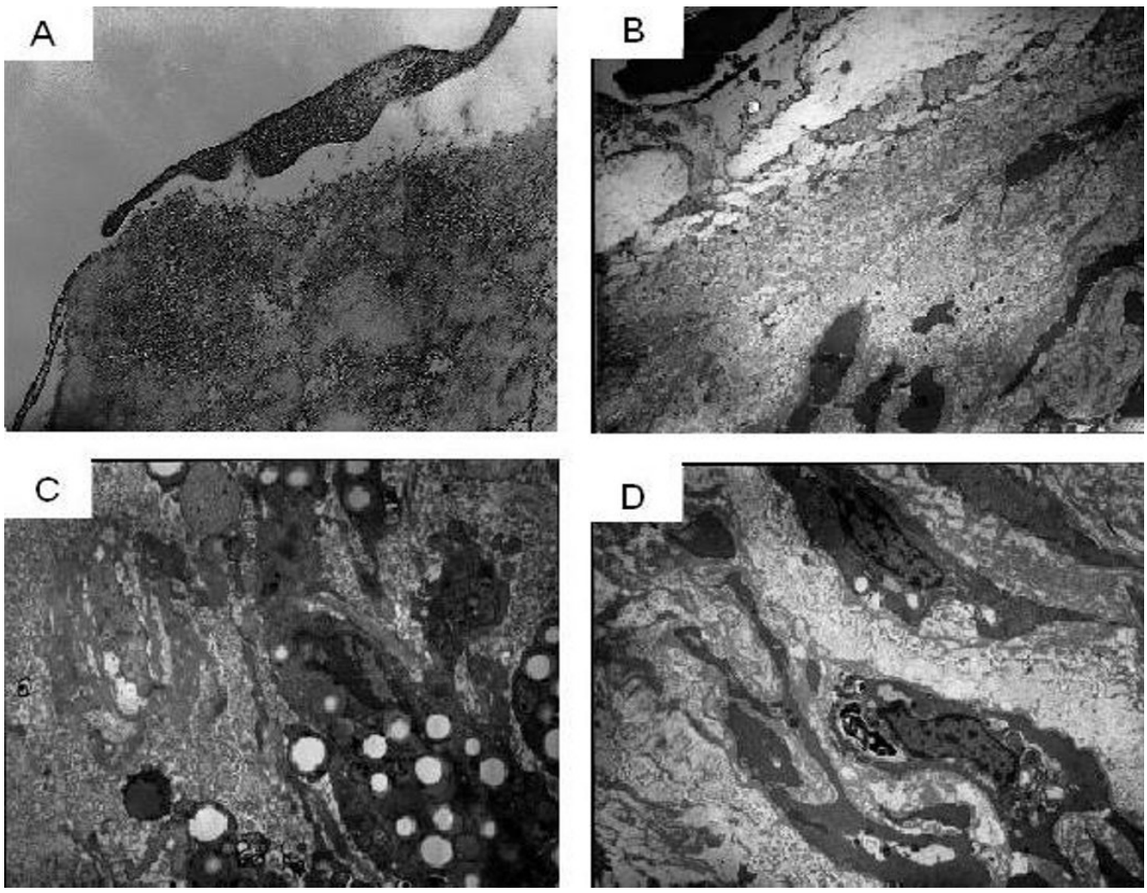

Fig. 10. Scanning electron microscope image - homograft with immunosuppression. A) Endothelial cells. B) Thickened elastic lamina of the intimal wall. C) Active myofibroblasts fagocyting lipids. D) Active myofibroblasts producing collagen

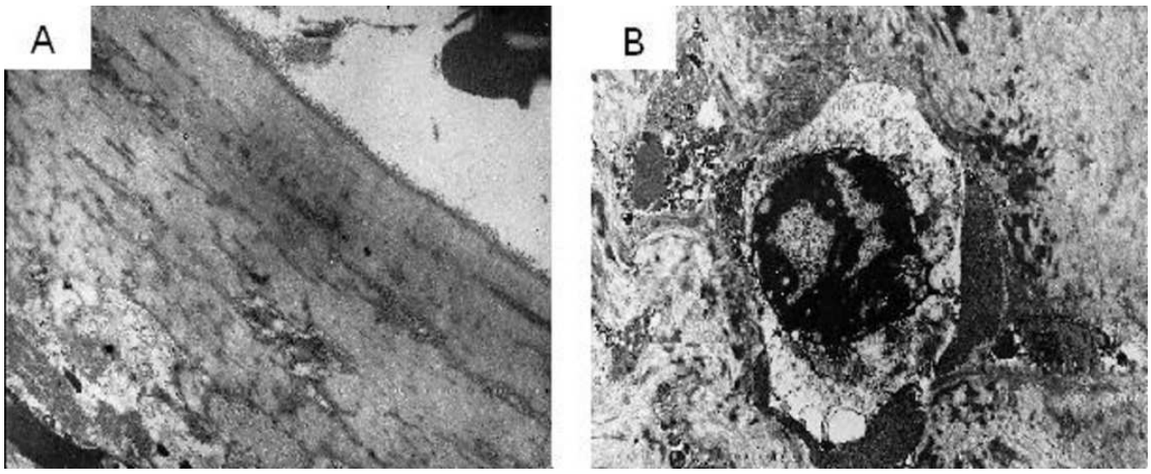

Fig. 11. Scanning electron microscope image - homograft without immunosuppression. A) Absence of endothelium. B) Apoptosis

4. Discussion

The infections of synthetic prostheses in our study were classified as third degree, according to the Szilagy scale, and fifth degree according to the Samson scale (Samson et al.,1988; Szilagyi et al.,1972). The replacement of the infected prosthesis with an arterial allograft was a reasonable solution in these life threatening conditions. We chose cold-preserved fresh arterial homografts because we believed the deep-freeze method was more likely to decrease long-term viability of the arterial wall and less likely to cause the degradation of the endothelium (Bujan et al.,2000; Desgranges et al.,1998; Manaa et al.,2003; Pascual et al.,2001, 2002; Vischjager et al., 1996a, 1996b).

Some scientists claim that the arterial homograft is characterized by low immunogenity and maintain that the graft rejection process is inconsiderable and does not cause an impaired functioning and survivability of the graft (Mirelli et al.,1998, 1999). This is why some vascular surgery centers transplant the arteries without the selection of ABO and HLA compatible donors. There are also numerous research studies showing that the usage of fresh arterial homografts with a preserved endothelium is associated with the immunological response of the graft recipient. This suggests the importance of the selection of donors of the same blood type and similar HLA histocompatibility when fresh arterial allografts are to be used (Chiesa et al.,1998; da Gama et al.,1994; Mirelli et al.,1998, 1999; Prager et al.,2002). We believe that in life threatening infections, the transplantation of the artery despite a slightly positive cross-match is acceptable. In this situation, the usage of immunosuppressive drugs is reasonable. However, we agree that the ABO compatibility is essential (Bracale et al.,1999; Chiesa et al.,1998; Prager et al.,2002).

Clinical trials show that there are changes in an arterial homograft's wall typical for a chronic rejection process (Allaire et al.,1994; Bandyk et al.,2001; Mirelli et al.,1999; Ruotolo et al.,1997). Immunosuppressive treatment can help to stop the degradation of the arterial wall and prolong its viability (Vischjager et al.,1996a, 1996b). However, there is still a question of whether or not to use these drugs in the presence of the infection.

Prolonged functioning of the arterial graft in patients treated with the immunosuppressive drugs was confirmed in some experimental trails (Deaton et al.,1992; Miller et al.,1993; Vermassen et al.,1991; Vischjager et al.,1996). In his experimental trial, Azuma et al. observed that lack or discontinuation of the intake of immunosuppressive medications caused the degradation of the arterial graft’s wall and loss of the endothelial cells (Azuma et al.,1999). It was also proven that insufficient dosages of these drugs caused an impaired functioning of the transplanted artery (Gabriel et al.,2002; Geerling et al.,1994; Stoltenberg et al.,1995).

In our study, the increase in activity of CD3+ and CD4+ lymphocytes and the decrease in activity of CD8+ lymphocytes (probably caused by the increase of the infiltration of the homograft's wall by these cells) in transplanted patients suggest arterial allograft's antigenicity.A larger decrease in CD3+ and CD4+ lymphocyte activity and a smaller decrease in CD8+ lymphocyte activity were observed in patients treated with Cyclosporine A than in those treated without immunosuppression. We assume that this was caused by the reduced immunological response of T helper lymphocytes (CD4+) and a smaller infiltration of the allograft by cytotoxic lymphocytes (CD8+). We also believe that this mechanism could help to keep the arterial wall undamaged (Mirelli et al.,1998, 1999).

One month of an antibiotic therapy and the replacement of the infected prosthesis with an arterial homograft lead to the remission of the infection despite the immunosuppressive

treatment in almost all patients. This was confirmed with radiological examinations, mainly scintigraphy, using Technetium-99m labeled leucocytes. The maintenance of a small accumulation of the labeled leucocytes around the homograft can be regarded as a chronic reaction against the foreign tissue. We stopped administering the antibiotics according to the scintigraphy results. Prolonged antibiotic and cyclosporine A therapy did not cause any complications associated with decreased immunity. We assume that the application of immunosuppressive drugs reduced the immunological response of the patients against transplanted grafts.

In patients who received immunosuppressive drugs no graft aneurysms were observed compared to 5 cases (19%) of this complication in patients without this therapy. Cyclosporine A may have helped to stop the degradation process of the arterial wall and thus prevented its aneurismal dilatation. The number of cases of postoperative infections was even smaller in those who received immunosuppressive medications. Our study suggests that profits from reasonable immunosuppression outweigh the risk of potential infection in patients with an arterial homograft implanted due to infection of a vascular prosthesis.

5. Conclusions

We believe that Cyclosporine A helped to stop the processes of damaging the graft's wall. Patients treated with this drug had fewer late postoperative complications. Our study suggests that cyclosporine A can be used in patients with an infection of a synthetic vascular prosthesis, undergoing the implantation of a fresh arterial allograft. We found out that fresh arterial homografts may be immunogenic in an extent which leads to its chronic rejection by the patient's immunological system. The results support the hypothesis that Cyclosporine A may prevent the autoimmunologic response of the patient and reduce the risk of damaging the arterial homograft.

Our study was carried out on a relatively small group of patients and it could be the reason why some of the differences between both examined groups of patients failed to reach statistical significance. Therefore, a multicentre randomized trial is needed to definitively establish the role of immunosuppression in the treatment of prosthetic vascular graft infections with the use of arterial homografts.

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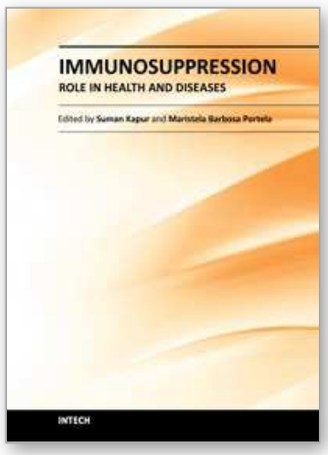

Immunosuppression - Role in Health and Diseases

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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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